^{60}CO ORBITAL RADIOTHERAPY IN GRAVES' OPHTHALMOPATHY

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ABSTRACT

PURPOSE: Graves' ophthalmopathy (GO) is a common cause of morbidity in patients with Graves' disease which suboptimal management is widespread. Immunosuppressive drugs and orbital irradiation represent treatment options for patients with moderate to severe and active GO. The aim of this study is to share our initial results from the application of orbital radiotherapy in GO.

MATERIAL AND METHODS: Fifteen consecutive patients (12 women and 3 men) at a mean age 52 years (range, 26 to 62 years) with GO underwent radiotherapy of posterior orbit. Research team included a radiotherapist, endocrinologist and ophthalmologist performing the first and the follow-up examinations. Both orbits were examined for soft tissue and cornea involvement, proptosis, eye muscle impairment, visual acuity, visual fields and tonometry. Ophthalmic index was calculated before and after treatment. All the patients had received glucocorticoids before radiotherapy as 46,67% of them required corticosteroids during the period of irradiation and 80% received antithyroid medication. Overall clinical response was evaluated as excellent, good, fair or no response according to Donaldson's criteria.

RESULTS: Fifteen patients completed the study with a follow-up of two or more months. All of them received 20 Gy to both orbits. The overall clinical response was excellent in two patients (13,33%), good in seven (46,67%), fair in five (33,33%), and there was no response in one patient (6,67% of the cases). The mean ophthalmopathy index (OI) was 7,2 before treatment and 3 after irradiation. There was a mean OI improvement of 4,2 points (range 2-7) compared to the pretreatment values. Best response was achieved for corneal involvement, soft tissue symptoms, sight loss and eye muscle impairment, while the response for proptosis was limited. No late adverse effects associated with radiotherapy such as cataract and radiation-induced retinopathy were observed at all.

CONCLUSION: Our study proved that orbital radiotherapy is an effective and safe treatment option for progressive GO with better results in the early and acute stage of the disease.

Key words: *Graves' ophthalmopathy, orbital radiotherapy, ophthalmopathy index, overall response, proptosis*

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INTRODUCTION

Graves' ophthalmopathy (GO) develops in 20-40% of the patients with Graves' disease (11). Most of them do not require intensive treatment and watchful waiting is a better approach. There is a spontaneous regression in cases with mild symptoms (9). However, 5-15% of the patients present with moderate to severe manifestations connected with sight threatening

symptoms such as progressive and persistent disease, severe inflammatory signs, severe dyplopia, corneal exposure, optic nerve compression, or increased ocular tension. These patients require intensive treatment (1,3).

Recent studies on GO pathogenesis support the hypothesis of autoimmune reaction against a shared or a cross-reactive thyroid orbit antigen. Orbital fibroblasts activated by T-lymphocytes produce glycosaminoglycans and their accumulation causes tissue edema and increases orbital volume. Radiation therapy has been used to treat thyroid eye disease with recognition of its antiinflammatory effect (2,6). Two other major treatment modalities are corticosteroids and surgical decompression (4,7). Immunosuppressive drugs, immunoglobulins, plasmapheresis and octreotide have been proposed, too (3,10).

Guidance on retrobulbar irradiation for thyroid eye disease from the National Institute for Health and Clinical Excellence (NICE) concludes that current evidence on the safety and efficacy of retrobulbar irradiation for thyroid eye disease appears adequate to support the use of this procedure in patients for whom other treatments are inadequate or associated with significant side effects.

This study reports our initial results from the application of orbital radiotherapy mainly in GO non-responders or GO patients in whom corticosteroid therapy is contraindicated.

MATERIAL AND METHODS

For a period of one year, sixteen consecutive patients with moderate to severe GO underwent radiotherapy of posterior orbit in the Department of Radiotherapy, Regional Oncological Hospital of Shoumen. Eligibility criteria included a more than two-month-long follow-up and a complete ophthalmic examination to calculate ophthalmopathy index (OI) before and after treatment. One patient was excluded from the analysis due to insufficient follow-up duration, less than one month while the rest 15 patients completed the study. There were 12 women and 3 men aged between 26 and 62 years (mean age of 52 years). Ophthalmopathy duration ranged between 6 and 26 months (mean duration of 10 months). Thyroid function assessment during radiotherapy revealed hyperthyroidism in 12 patients (80%) while two patients (13,33%) were euthyroid and one patient (6,67%) was hypothyroid. All the patients were previously given local and systemic corticosteroids for the ophthalmopathy, seven patients (46,67%) required corticosteroids during the period of radiotherapy and 12 patients (80%) received antithyroid medication. Surgery had been applied in the rest three patients (20% of the cases). Two patients (13,33%) had a history of cataract and one patient was operated on for glaucoma before radiotherapy.

A multidisciplinary team including a radiotherapist, an endocrinologist and an ophthalmologist performed the first and the subsequent examinations. Both orbits were examined for signs of proptosis displacement of the globe and by tonometry. The ocular fundus, visual acuity, visual fields and eye movements were assessed, too. We used ultrasound and CT scanning to clearly delineate orbital structures. Eye changes were numerically scored according to OI criteria of Stanford Scoring System (Table 1). Patient's ophthalmological status was examined prior to, one and two months after treatment as well as every three months thereafter. Overall clinical re-

Table 1. OI criteria according to Stanford Scoring System

Grade	Soft tissue	Proptosis (mm)	Eye muscle impairment	Cornea	Vision
1.	slight redness, chemosis, edema, minimal symptoms	20-23	infrequent diplopia, not in primary gaze	slight stippling	20/25-20/40
2.	moderately severe redness, chemosis, edema, moderate symptoms	24-26	diplopia, moderate movement limitation	moderate stippling and symptoms	20/45-20/100
3.	conjunctival reduncy, marked edema, severe symptoms	>27	severe constant muscle dysfunction	ulceration	<20/100

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sponse was evaluated as excellent, good, fair or no response according to Donaldson's criteria. In the evaluation of the therapeutic results for each ophthalmic parameter, complete response (CR) was defined as complete improvement (grade 0) according to Stanford Scoring System criteria. Partial response (PR) was defined as certain reduction of grade and no response (NR) as no change of grade.

Patients were treated in supine position using individual immobilization devices (Fig. 1).

Fig. 1. Individual immobilization device during ^{60}Co radiotherapy

The margins of the bony orbit, lens position and pituitary fossa were drawn on to the outline using CT scan data and lateral simulator films. For irradiation of the posterior orbit, a pair of lateral ^{60}Co half-beam block fields with custom shielding was used to reduce the dose to the healthy tissues (Fig. 2). A typical dose distribution was presented on Fig. 3. Dose prescription at the isocentre of the formed fields at the mid depth was 20 Gy in 10 fractions given in two weeks.

RESULTS

Fifteen patients followed-up for two or more months were eligible for analysis. All of them received 20 Gy to both orbits. All the patients had been referred because of progressive eye symptoms or life threatening complication after a high

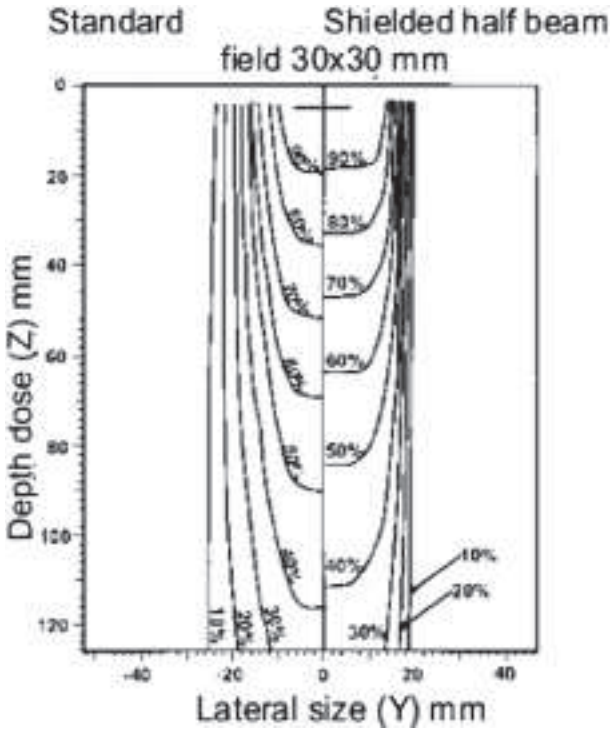

Fig. 2. Lateral ^{60}Co half-beam block fields used to reduce the dose in the healthy tissues during posterior orbit irradiation

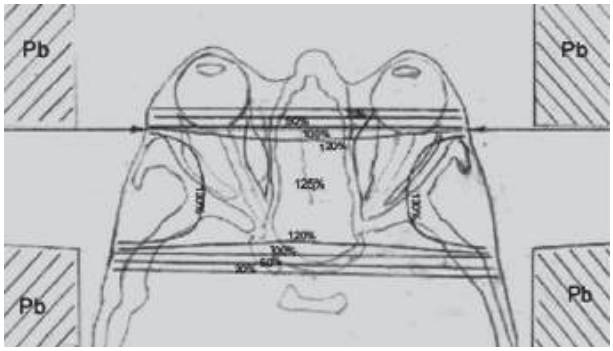

Fig. 3. Dose distribution in the treatment area

cumulative dose of corticosteroids (5) including two hemorrhages from gastric ulcer, one diabetes mellitus with worsening control, one patient of hypokaliemia with paroxysmal tachyarrhythmia, and one deep vein thrombosis of the leg. According to the leading eye symptoms, the patients were subdivided in the following groups: 93% with progressive soft tissue symptoms, 100% with proptosis, 93,33% with restriction of the gaze, 80% with eye muscle impairment, 53,33% with corneal abnormalities, and 46,67% with worsening vision.

Table 2. Comparison of initial and final OI (n=15)

Variable	n	Initial score (mean and range)	Final score (mean and range)	Change and % of initial score
soft tissue	14	2,2 (2-3)	0,8 (0-2)	-1,4 (64%)
proptosis	15	2,3 (1-3)	1,3 (0-3)	-1,0 (43%)
eye muscle	14	1,6 (1-3)	0,6 (0-1)	-1,0 (63%)
cornea	8	1,1 (1-2)	0,2 (0-1)	-0,9 (82%)
vision	8	1,5 (1-3)	0,5 (0-2)	-1,0 (67%)
total score	15	7,2 (4-12)	3,0 (0-7)	-4,2 (58%)

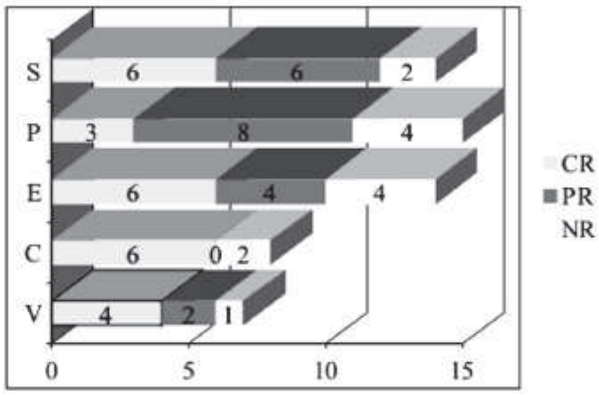

Fig. 4. Treatment response for each ophthalmic parameter: S (soft tissue symptoms), P (proptosis), E (eye muscle impairment), C (corneal involvement), V (vision loss)

Patient's responses as a function of each pathological parameter two months after radiotherapy were summarized in Table 2. The overall clinical response was excellent in two patients (13,33%), good in seven (46,67%), fair in five (33,33%), and there was no response in one patient (6,67% of the cases). A rapid improvement after treatment which occurred in some cases with excellent and good results was associated with short GO duration. Mean OI was 7,2 before treatment and 3 after irradiation. There was a mean OI improvement of 4,2 points (range 2-7) compared to the pretreatment values.

At the time of radiotherapy, seven patients were on corticosteroids, but only one patient was continuing this treatment at the last following-up visit. Six out of seven patients with increased intraocular tension before radiotherapy improved and five of them had normal tension without any medication. None of ten patients with a relatively long following-up of 6-15 months presented with recurrence of any eye symptoms. Proptosis was slightly improved in two patients after 8 and 10 months, respectively.

Treatment response for each ophthalmic parameter was presented in Table 2 and Fig. 4. Out of 14 patients with soft tissue symptoms before radiation, six showed CR, six showedd PR, and two showed NR. The mean initial soft tissue score decreased by 64%, from 2,2 to 0,8. All the patients had proptosis before radiotherapy and only three of them had CR, eight had PR and four had NR. The mean initial proptosis score decreased less than the soft tissue one - by 43%, from 2,3 to 1,3. Eye muscle impairment occurred in 14 patients. Six patients achieved CR, four - PR and four - NR. Corneal involvement and vision loss were observed in eight and seven patients, respectively while CR was achieved in six and four patients, PR in zero and two ones, and NR in two patients and one patient, respectively. The best response was observed for corneal involvement, soft tissue signs, vision loss and eye muscle impairment, while the response for proptosis was limited. Neither late adverse effects, nor complications associated with radiotherapy such as cataract and radiation-induced retinopathy were registered at all.

DISCUSSION

Our results from the application of posterior orbit irradiation in the patients with progressive and acute GO indicate that this method provides an effective and prompt regression of major symptoms after unsatisfactory response to corticosteroid therapy. We applied the scoring system of Stanford University in spite of criticism by several authors (3,9).

The best response to irradiation is in the categories of soft tissue and corneal findings. This is in

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concordance with other authors' results (6,8,10). Soft tissue symptoms improve in 87% of our patients with relatively short following-up. There is an improvement or stabilization of proptosis in 73% of the cases. There is improvement or stabilization of the eye muscle impairment, corneal findings, and vision in 71%, 75%, and 86% of the patients, respectively.

Larger trials with long-term following-up demonstrate subjective and objective improvement one year or even more after the irradiation. Our preliminary results are encouraging and we expect the clinical response to the radiotherapy to be completely manifested with time. For this reason, ophthalmic surgery should be withheld until patients demonstrate a plateau in their response to radiotherapy (5,10).

Besides our results prove that the patients at the early stage of the disease more likely achieve excellent or good therapeutic results than those with more advanced symptoms and longer history. There is a correlation between the objective response, i. e. low final OI score and the subjective one, i. e. patient's satisfaction, too.

Our subgroups with or without glucocorticoid treatment are too small to conclude which treatment approach is superior: concomitant radiation and corticosteroids or radiotherapy alone. The combination of these treatment modalities is considered more effective than either treatment alone, however, randomized clinical trials are still lacking (12).

CONCLUSION

Our study reveals that orbital radiotherapy is an effective and safe treatment option for progressive GO, with 93% overall response rate, the same patient satisfaction rate, and without any acute and long-term complications. This method should be used more often and at the early and acute stage of the disease.

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